32

Biological and Pharmacological Aspects of the Treatment of PTSD

Matthew J. Friedman

INTRODUCTION

From a biological psychiatric perspective, research on post-traumatic stress disorder (PTSD) has recently entered a new phase. The first phase, ushered in by Blanchard et al., (1982) established, beyond doubt, that PTSD is associated with psychophysiological and neurobiological abnormalities. Such findings led to a rediscovery of Abram Kardiner's prescient and seminal work with World War I veterans (1941); Kardiner and Spiegel (1947) stimulated further research and generated a number of provocative theoretical models (see reviews by Kolb, 1987, 1988; Kosten and Krystal, 1988; Bremner, Southwick, and Charney, 1991; van der Kolk, 1987a; Friedman, 1991). Of particular importance was the suggestion that well-studied experimental chronic stress animal models, such as learned helplessness/inescapable stress (Seligman and Beagley, 1975), kindling (van der Kolk, 1987a; Friedman, 1988), and potentiated startle (Davis, 1990), might be specifically applicable to an understanding of the PTSD syndrome.

Based on these theoretical perspectives, the new phase in PTSD research consists of hypothesis-driven studies in which clinical cohorts participate in elegant experimental paradigms derived from animal research. This approach improves efforts to explicate the specific neurobiological abnormalities associated with PTSD. With the aid of such biochemical and pharmacological strategies, researchers now have a much better understanding of the central adrenergic, hypothalamic-pituitary-adrenocortical (HPA) and endogenous opioid abnormalities associated with PTSD. Three other neurobiological systems, serotonergic, dopaminergic, and GABA-benzodiazepine, known to be disrupted in animals exposed to inescapable stress, kindling, or fear-potentiated startle paradigms

Table 32.1
Physiological Alterations Associated with PTSD

1. Heightened Sympathetic Arousal.
   a. Elevated resting heart rate and blood pressure
   b. Increased reactivity to neutral stimuli
   c. Increased reactivity to traumamimetic stimuli
2. Exaggerated Startle Response
   a. Lowered threshold
   b. Increased amplitude
   c. Loss of startle inhibition
3. Disturbed Sleep and Dreaming
   a. Poor quality of sleep 1) increased sleep latency, 2) decreased sleep time, 3) increased movement, 4) increased awakenings
   b. Possible abnormalities in sleep architecture (decreased slow wave sleep)
   c. Traumatic nightmares are unique
4. Abnormal Evoked Cortical Potentials
   a. Reducer pattern in response to neutral stimuli

(Charney, Southwick, and Krystal, in press), are just beginning to receive attention in clinical PTSD research. Obviously, the better the understanding of how specific neurotransmitter systems are dysregulated in PTSD, the better the chances of identifying specific drugs that might be expected to alleviate the symptoms of PTSD.

In addition to this hypothesis-driven search for effective pharmacotherapeutic agents, there is a growing body of empirical research in which a variety of drugs have been assessed for efficacy in PTSD. Most drugs tested so far have either been antidepressants or anxiolytics, with a few interesting exceptions such as clonidine, propranolol, carbamazepine, and valproate. Besides offering useful information on drug efficacy, these studies have provided data that contribute to theoretical efforts to conceptualize PTSD.

This chapter begins with a brief review of research findings on psychophysiological and neurobiological alterations associated with PTSD. It then reviews those results in the context of pathophysiological models pertinent to drug treatment of PTSD. Next, it reviews the current clinical psychopharmacological literature with regard to findings on drug efficacy, methodological concerns, and important unanswered questions and, finally, makes some recommendations for future research.

BIOLOGICAL ALTERATIONS ASSOCIATED WITH PTSD

Several symptoms diagnostic for PTSD, as delineated in the *Diagnostic and Statistical Manual* (DSM III-R; APA, 1987) and ICD-10 (World Health Organization, 1993) have been operationalized and reproduced in psychophysiological laboratories. As shown in Table 32.1, these include heightened sympathetic

arousal, exaggerated startle response, disturbed sleep and dreaming, and abnormal evoked cortical potentials.

Among Vietnam combat veterans with PTSD, pulse rate and blood pressure appear to be consistently elevated in the resting state (as reviewed by Blanchard, 1990). Furthermore, PTSD patients exhibit greater cardiovascular arousal following exposure to either a neutral stimulus, a burst of white noise (Paige et al., 1990), or a meaningful traumamimetic stimulus such as the sounds or images of combat (Blanchard et al., 1982; Kolb, 1987; Malloy, Fairbank, and Keane, 1983; Pitman et al., 1987; McFall et al., 1990).

Vietnam war zone veterans with PTSD exhibited both a lowered threshold and increased amplitude of the acoustic startle eyeblink reflex in comparison to a control group of Vietnam war zone veterans without PTSD (Butler et al., 1990). With a related but more complex experimental protocol testing the eyeblink reflex, children with PTSD showed an age-related loss of startle inhibition in comparison to appropriate controls (Ornitz and Pynoos, 1989).

Disturbed sleep and dreaming have been considered a hallmark of PTSD (Kardiner and Spiegel, 1947; Archibald and Tuddenham, 1965; Horowitz, Wilner, and Alverez, 1979). Without doubt, PTSD patients exhibit difficulty initiating and maintaining sleep, show excessive movement during sleep, and demonstrate increased nocturnal awakenings (Friedman, 1988; Ross et al., 1989; ver Ellen and von Kammen, 1990; Rosen et al., 1991). Furthermore, there is considerable evidence that traumatic nightmares are unique phenomena that differ from classic nightmare/night terror, Stage 4 episodes, as well as from the dream anxiety attacks associated with rapid eye movement (REM) sleep (Friedman, 1981; Ross et al., 1989). It is controversial at this time, however, whether PTSD is associated with characteristic changes in sleep architecture. Inconsistent findings from sleep laboratory research in this regard may be due to a variety of methodological problems, such as small sample sizes, diagnostic imprecision, medication status, and diagnostic comorbidities (Friedman, 1991; ver Ellen and von Kammen, 1990). Preliminary sleep laboratory findings on forty Vietnam veterans with PTSD (Woodward, personal communication, 1992) suggested that PTSD may be associated with a marked reduction in slow-wave sleep.

The final psychophysiologic abnormality reported among PTSD patients is a single report by Paige and associates (1990) on the pattern of cortical evoked potentials elicited by auditory stimuli. In contrast to combat-exposed controls, Vietnam veterans with PTSD showed a reduced, rather than normal or augmented, pattern (Buchsbaum, 1976). The author suggested that these findings might indicate that PTSD patients are reducers in whom inhibitory feedback loops are activated to dampen a tonic state of hyperarousal.

Abnormal neurohumoral and neuroendocrinological abnormalities associated with PTSD are particularly pertinent to the search for effective pharmacotherapy. On one hand, they tie findings with PTSD patients more directly to neurobiological animal research with chronic stress paradigms. On the other hand, these results suggest specific categories of drugs to test in PTSD patients. As shown

Table 32.2
Neurohumoral/Neuroendocrinological Abnormalities Associated with PTSD

1. Adrenergic Hyperactivity
   a. Higher resting levels of urinary catecholamines
   b. Elevated catecholamine levels following traumamimetic stimuli
   c. Down regulation of alpha–2 and beta adrenergic receptors
   d. Yohimbine-induced panic and flashbacks
2. Hypothalamic-Pituitary-Adrenocortical Axis Abnormalities
   a. Decreased urinary free cortisol levels
   b. Increased glucocorticoid receptors
   c. Supersensitivity to dexamethasone
   d. Blunted ACTH response to CRH
3. Opioid System Dysregulation
   a. Lower pain threshold at rest
   b. Stress induced analgesia
   c. Lower beta-endorphin levels
   d. Abnormal met-enkephalin release and metabolism

in Table 32.2, current research suggests that PTSD is associated with adrenergic hyperactivity, HPA axis abnormalities, and opioid system dysregulation.

Many independent observations suggest that PTSD is associated with a hyperadrenergic state. Consistent with heightened sympathetic nervous system activity indicated in Table 32.1 is the finding that PTSD patients have higher resting, 24-hour urinary epinephrine and norepinephrine levels than normals and patients with most other psychiatric disorders (Mason et al., 1986; Kosten et al., 1987). Second, war zone Vietnam veterans with PTSD show significantly greater increases in plasma norepinephrine and epinephrine levels following exposure to traumamimetic stimuli reminiscent of combat sounds in contrast to combat veterans without PTSD (Blanchard et al., 1991; McFall et al., 1990).

If, as suggested by both of these observations, PTSD is associated with higher levels of circulating catecholamines, such increased adrenergic activity should subsensitize or down-regulate adrenergic receptors. This, indeed, appears to be the case since the number of both alpha–2 and beta adrenergic receptor sites is reduced in platelets and lymphocytes of combat veterans with PTSD (Perry et al., 1990; Lerer et al., 1990).

Finally, evidence that there is a central nervous system (CNS) component to the PTSD hyperadrenergic state comes from experiments with yohimbine, a centrally acting alpha–2 antagonist that can precipitate panic reactions, in panic-disordered patients (Charney et al., 1987). When Vietnam combat veterans with PTSD were given yohimbine in a double-blind experimental protocol, 60 percent of them exhibited hyperarousal, anxiety, panic, and intrusive recollections of traumatic combat experiences. In 40 percent of these patients, yohimbine elicited

frank flashback (dissociative) episodes (Southwick, Krystal, et al., 1992). It should be noted that yohimbine has no such effects on normal controls free of panic disorder and/or PTSD.

Turning to the HPA axis, it appears that PTSD is associated with a specific abnormality that clearly distinguishes it from major depressive disorder and other DSM III-R diagnoses. Mason et al. (1986) reported that urinary free cortisol levels are lower in PTSD patients than in other psychiatric diagnostic groups. The major pathophysiological change appeared to be an excessive number of glucocorticoid receptors (Yehuda, Lowy, et al., 1991). Based on this finding, Yehuda and associates hypothesized that PTSD is associated with HPA glucocorticoid supersensitivity and predicted that PTSD patients would show excessive sensitivity to the glucocorticoid dexamethasone. Indeed, as predicted, Yehuda, Giller et al. (1991) elegantly demonstrated complete HPA suppression in PTSD patients with a 0.5-milligram (and in some cases a 0.25-milligram) dose of dexamethasone, a dose that is unable to suppress the HPA axis in normal controls. (It should be recalled that the HPA abnormality in depression is exactly the opposite. Depressed patients show glucocorticoid receptor subsensitivity as manifested by nonsuppression of the HPA system with 1.0 milligram dexamethasone). From a practical point of view, these results suggest that the dexamethasone suppression test (DST) may play an important diagnostic role in future PTSD research and treatment, if it continues to differentiate PTSD supersensitivity/suppression from depressive subsensitivity/non-suppression (Kudler, Davidson, and Meador, 1987; Halbreich et al., 1988; Olivera and Fero, 1990; Kosten et al., 1990; Yehuda, Lowy, et al., 1991). The final HPA abnormality in PTSD is a blunted ACTH (adrenocorticotropin hormone) response to CRH (corticotropin-releasing hormone) in contrast to normal controls (Smith et al., 1989).

The third dysregulated neurohumoral system listed in Table 32.2 is the endogenous opioid system. Clinical reports of lower pain threshold (Perry et al., 1987) and increased susceptibility to chronic pain (Benedikt and Kolb, 1986; Wolf, Alavi, and Mosnaim, 1988) suggested that PTSD is associated with lower resting levels of endogenous opioids. This is supported by the laboratory finding that PTSD patients have lower resting beta-endorphin levels (Hoffman et al., 1989). Additional evidence for opioid system dysregulation is data suggesting that PTSD patients have a lower rate of release of met-enkephalin into the circulation than normal controls (Wolf et al., 1990).

The most dramatic opioid system abnormality, however, is that stress-induced analgesia (SIA) could be produced in Vietnam veterans with PTSD after exposing them to videotaped Vietnam combat scenes from the movie *Platoon*. Such exposure produced a significant elevation in pain thresholds that could be prevented by pretreatment with the narcotic antagonist naloxone (Pitman et al., 1990). This experiment is valuable for two reasons. First of all, it shows that SIA, a well-known phenomenon in animal research on chronic stress, can be reproduced in

PTSD patients. Second, it provokes speculation that endogenous opioid fluctuations may serve as the biological vehicle for some of the avoidant/numbing symptoms associated with PTSD (van der Kolk et al., 1989).

Five other neurohumoral findings should be noted. Serum testosterone levels are significantly higher in PTSD patients than in other psychiatric disorders (Mason et al., 1990). Second, PTSD patients show marked elevation in most thyroid hormones (total and free thyroxine and total and free triiodothyronine), compared with non-PTSD psychiatric controls (Mason et al., 1990). Third, PTSD patients were distinguishable from depressed patients because they showed a normal response to the thyrotropin-releasing hormone (TRH) stimulation test, in contrast to depressed patients, who exhibited a blunted response (Kosten et al., 1990). Fourth, recent rape victims (who were not diagnosed with respect to PTSD) showed a dramatic increase in urinary conjugated dopamine in contrast to appropriate controls (Ende, Gertner, and Socha, 1990). Finally, among sexually abused boys, the growth hormone response to clonidine, but not to L-dopa, was abnormally sensitive, whereas among physically abused boys, the growth hormone response was abnormally sensitive to L-dopa but not to clonidine (Jensen et al., 1991). Although PTSD was not assessed in this last experiment, the findings suggest that biological strategies may play an important role in delineating different subtypes of PTSD. The last two experiments invite comparisons with animal studies that demonstrate dopaminergic abnormalities following exposure to inescapable stress and suggest that there may be an etiologic rationale for the use of neuroleptic agents in PTSD.

ANIMAL MODELS

As noted previously, three animal models have been proposed for PTSD: inescapable stress, fear-potentiated startle, and kindling. Although an exposition on each of these models is beyond the scope of this chapter, it is instructive to briefly review each model's implications for pharmacotherapy.

The inescapable stress model (Seligman and Beagley, 1975; van der Kolk et al., 1985; Kosten and Krystal, 1988) directs attention to limbic system and locus coeruleus abnormalities. It suggests that the neurotransmitter systems dysregulated in PTSD are likely to be noradrenergic (Anisman and Zacharko, 1986; Weiss et al., 1981), dopaminergic (Kalivas and Duffy, 1989), GABA-benzodiazepine (Weizman et al., 1989; Medina et al., 1983), and opioid (Stuckey et al., 1989).

The fear-potentiated startle model (Davis, 1990) suggests that the activity of the central nucleus of the amygdala and its projections to the brain stem are likely to be disrupted in PTSD. Drugs that affect this system include noradrenergic agents, benzodiazepines, and opiates.

Finally, the kindling/long-term potentiation model postulates sensitization of limbic nuclei involved with emotional arousal, memory, and other behaviors. Kindling is associated with increased benzodiazepine receptor binding along with

sensitization of catecholaminergic neurons. Such a model suggests that anticonvulsants with antikindling potency might be effective in PTSD. It also suggests that clinical trials with benzodiazepines might be in order.

To bridge the chasm from theory to practice, basic research with PTSD patients and the animal models that have emerged from such research suggest that drugs affecting adrenergic, benzodiazepine, opioid, and, possibly, dopaminergic systems might be useful in PTSD. It also appears that the pathophysiology of PTSD may be exceedingly complex, with stable abnormalities in a number of interdependent systems. Such a possibility implies that successful pharmacotherapy for this disorder may require simultaneous administration of several drugs, each of which has a specific action on a specific neurobiological system.

There is also a growing interest in drugs that act primarily on serotonergic systems. It is apparent that among the growing family of serotonin receptors, several (5-HT1A, 5-HT2, 5-HT3) appear to mediate anxiety (Gonzalez-Heydrich and Peroutka, 1990). It is less apparent whether serotonergic activity has been altered in PTSD, as it has been in other anxiety disorders (such as obsessive-compulsive disorder). Perhaps the best evidence to date comes from preliminary experiments in which Vietnam veterans with PTSD experienced panic attacks and flashbacks after receiving the serotonergic agonist mCPP (m-chlorophylpiperazine) (Southwick, Yehuda et al., in press). Such findings, if replicated, would suggest that there might be an etiological basis for prescribing serotonergic agents in the treatment of PTSD.

DRUG TRIALS

Despite numerous published articles on open trials of different drugs in the treatment of PTSD, there have been very few controlled pharmacological trials. These consist of three controlled trials with tricyclic antidepressants (TCAs) (Frank et al., 1988; Davidson et al., 1990; Reist et al., 1989), two with monoamine oxidase inhibitors (MAOIs) (Frank et al., 1988; Shestatzky, Greenberg, and Lerer, 1988), one with the beta-adrenergic antagonist propranolol (Famularo, Kinscherff, and Fenton, 1988), and one with the triazolo-benzodiazepine, alprazolam (Braun et al., 1990). Several reviews catalog case reports and open trials with TCAs, MAOIs, sympatholytic agents (propranolol and clonidine), anxiolytics, carbamazepine, lithium, and neuroleptics (van der Kolk, 1987a; Friedman, 1988, 1991; Silver, Sandberg, and Hales, 1990). The comprehensive review by ver Ellen and van Kammen (1990) presented details on most open and closed drug trials through 1990. Since that time there have been reports on open trials with buspirone, fluoxetine, cyproheptidine, alprazolam, valproate, and TCA/clonidine combination therapy that have not been reviewed elsewhere. In general, the aforementioned reviews of published case reports and open trials indicated significant anti-PTSD efficacy for a variety of drugs. On the other hand, these same reviews concluded that results from controlled trials have been mixed. A common finding in almost all published reports, however, is that successful

pharmacotherapy for PTSD generally results in attenuation of DSM III-R intrusive recollections (especially nightmares) and arousal (especially insomnia, startle, and irritability) symptoms. Avoidant/numbing symptoms usually do not respond to medication. An exciting preliminary result in this regard, however, is that fluoxetine may reduce the severity of avoidant/numbing as well as the other PTSD symptoms (discussed later) (Davidson, Roth and Newman, 1991; McDougle et al., 1990).

Tricyclic Antidepressants and MAO Inhibitors

Based on the previous discussion, it would appear that any drug that can dampen physiologic hyperactivity, ameliorate the disturbed sleep/dream cycle, attenuate sympathetic hyperarousal, or reduce anxiety should be helpful in the treatment of PTSD. For these reasons, antidepressants, both TCAs and MAOIs, would appear to be good choices since they are effective anxiolytic and antipanic agents that can dampen sympathetic arousal through a variety of mechanisms (Kahn et al., 1986; Sheehan, Ballenger, and Jacobsen, 1980; Charney, Menkes, and Heninger, 1981).

A quantitative review of treatment outcomes from TCA pharmacotherapy—including open, as well as double-blind, trials—suggests that they effectively reduced specific PTSD symptoms such as hyperarousal, intrusive recollections, traumatic nightmares, and flashbacks (Southwick, Yehuda, et al., 1994). Furthermore, when depressive symptoms are monitored concurrently with PTSD symptoms, TCAs appear to have much greater efficacy against the former, suggesting that clinical success may have more to do with an antidepressant than an anti-PTSD effect (for references, see ver Ellen and von Kammen, 1990; Friedman, 1991).

The three published double-blind trials of TCAs reported mixed results and are somewhat difficult to interpret. Frank et al. (1988) in an eight-week double-blind comparison of imipramine (a TCA), phenelzine (a MAOI), and placebo in thirty-four Vietnam combat veterans with PTSD found significant reduction in intrusion but not avoidant symptoms as measured by the Impact of Events Scale (IES) (Horowitz, Wilner, and Alverez, 1979). Davidson et al. (1990), using the IES in an eight-week double-blind comparison of amitriptyline versus placebo in forty-six Vietnam veterans with PTSD, reported modest reductions in PTSD symptoms. It is noteworthy that the data also show a small reduction in avoidant symptoms for PTSD patients. Davidson and associates also observed that depressed PTSD patients appeared to show greater remission than non-depressed patients. They suggested that improvement was most likely attributable to amitriptyline's antidepressant and anxiolytic potency rather than to a specific anti-PTSD effect. Finally, Reist et al. (1989) reported no difference between the TCA desipramine and placebo in a four-week double-blind comparison.

The two MAOI studies, both with phenelzine, also have contradictory results. In the imipramine, phenelzine, placebo eight-week double-blind trial by Frank

et al. (1988), mentioned earlier, phenelzine was superior to imipramine (and both were significantly more effective than placebo) in reducing intrusive symptoms such as nightmares, intrusive recollections, and flashbacks, as measured by the IES. (It should be noted that since the IES does not monitor hyperarousal symptoms, we have no information on this important component of the PTSD syndrome in any of these double-blind trials with TCAs and MAOIs.) Finally, a four-week double-blind crossover comparison between phenelzine and placebo showed no difference between the two treatments with regard to PTSD symptom reduction (Shestatzky, Greenberg, and Lerer, 1988).

Kudler et al. (1989) criticized the two negative studies (Reist et al., 1989; Shestatzky, Greenberg, and Lerer, 1988) on several methodological grounds. Based on their criticism, it is recommended that any drug trial in PTSD be carried out for a minimum of eight to ten weeks; that a better instrument than the IES be used in future drug trials; and that future research designs include adequate controls for disorders frequently comorbid with PTSD such as major depressive disorder (MDD) (Reaves, Hansen, and Whisenand, 1989) and alcoholism/substance abuse (Kofoed, Friedman and Peck, 1993). With regard to MDD, it is possible that recent findings by Yehuda, Giller, et al., 1991 and Yehuda, Lowy, et al., 1991 on different HPA axis abnormalities in PTSD and MDD may enable future researchers to identify and separate patients with PTSD-alone from patients with PTSD + MDD. Such a separation will make it possible to determine whether TCAs and MAOIs have a specific anti-PTSD action or whether their efficacy is due to their antidepressant and anxiolytic properties.

Clonidine and Propranolol

There are theoretical and practical reasons that drugs that antagonize adrenergic activity might prove to be effective agents in PTSD treatment. Research cited previously indicates that sympathetic hyperarousal and adrenergic dysregulation occurs in PTSD patients (Tables 32.1 and 32.2). Second, adrenergic abnormalities are detectable in all three of the animal models (inescapable shock, fear-potentiated startle, limbic kindling) proposed for PTSD. Finally, since MAOIs and TCAs are very potent antipanic agents and since panic disorder is an adrenergic dysregulation syndrome (Charney et al., 1987), the effectiveness of TCAs and MAOIs in PTSD may be attributable to their antiadrenergic antipanic/anxiolytic properties.

Clonidine is an adrenergic alpha–2 agonist, and propranolol is a postsynaptic adrenergic beta-blocking agent. Both drugs reduce sympathetic arousal and anxiety through different mechanisms of action (Tanna, Penningroth, and Woolson, 1977; Charney et al., 1986; Ravaris et al., 1991). There has been surprisingly little interest in either clonidine or propranolol despite the fact that Kolb, Burris, and Griffiths (1984) reported several years ago that in open trials on Vietnam veterans with PTSD, both drugs effectively reduced PTSD symptoms such as nightmares, intrusive recollections, hypervigilance, insomnia, startle reactions,

and angry outbursts. Kinzie and Leung (1989) conducted an open trial of clonidine in combination with the TCA imipramine in Cambodian refugee patients suffering from both PTSD and depression. They reported that PTSD symptoms such as insomnia, nightmares, and startle reactions (as well as depressive symptoms) improved in most patients. There are also other reports that the clonidine/imipramine combination was effective in treating Southeast Asian refugees with PTSD (Friedman and Jaranson, in press).

Although propranolol was ineffective in an open trial with Cambodian refugees with PTSD (Kinzie, 1989), it had marked efficacy in American children with acute PTSD who had been physically and/or sexually abused (Famularo, Kinscherff, and Fenton, 1988). In an A-B-A design (off-on-off medication), eight out of eleven children receiving 2.5 milligrams/kilogram/day exhibited significant reductions in PTSD intrusion and arousal symptoms during the active drug phase of this clinical trial. Furthermore, when placebo was substituted for propranolol, all symptoms returned with the same intensity as before.

Benzodiazepines

Use of benzodiazepines in PTSD is controversial, despite their proven efficacy as anxiolytics. In some settings up to 71 percent of PTSD patients have received benzodiazepines (Ciccone et al., 1988) while in other settings clinicians are very reluctant to prescribe these drugs because of the risk of addiction/dependency among patients who already have very high rates of alcoholism and chemical abuse/dependency (Kofoed, Friedman, and Peck, 1993). In the case of alprazolam, these concerns are augmented by the additional risk of rebound anxiety and severe withdrawal symptoms (Higgitt, Lader, and Fonagy, 1985; Noyes et al., 1985). In fact, Risse et al., (1990) reported on eight Vietnam veterans who experienced severe exacerbation of their PTSD symptoms during alprazolam withdrawal. The patients exhibited anxiety, sleep disturbance, rage reactions, hyperalertness, increased nightmares, intrusive thoughts, and homicidal ideation.

Despite these reservations, benzodiazepines in general are excellent anxiolytics, and alprazolam, in particular, has potent anxiolytic/antipanic actions. Furthermore, the kindling model of PTSD offers a theoretical reason to consider these drugs since limbic kindling is associated with increased benzodiazepine receptor binding (McNamara et al., 1985; Morita et al., 1985; Tietz, Gomaz, and Berman, 1985). There are two published reports on alprazolam in PTSD treatment. Feldman (1987) conducted an open trial and found that sixteen out of twenty veterans with PTSD treated with alprazolam showed reduced insomnia, anxiety, irritability, and hyperarousal. Evidence for benzodiazepine-induced emotional disinhibition is indicated, however, by Feldman's report that four of these patients showed an increase in outbursts of anger. Braun et al. (1990) carried out a randomized double-blind five-week crossover trial of alprazolam versus placebo on Israeli patients with PTSD. Although there was a general

reduction in anxiety level during alprazolam treatment, the drug had no effect on specific PTSD symptoms.

Antikindling Agents

Carbamazepine and valproate are two antikindling agents with reported efficacy in treatment of PTSD. Kindling is a relatively stable neurobiological alteration that has been hypothesized to develop after exposure to traumatic stress (van der Kolk, 1987a; Friedman, 1988). It is a process by which neuroanatomic structures, especially those in the limbic system, become increasingly sensitized following exposure to electrical stimulation or stimulant (cocainelike) drugs. Once established, kindling can lead to profound CNS disruption as manifested by neurophysiological abnormalities, grand mal seizures, and aberrant behavior. Post and Kopanda (1976) invoked kindling as a model for lithium-refractory bipolar affective disorder. Van der Kolk (1987a) and Friedman (1988) independently suggested that the chronic CNS sympathetic arousal associated with PTSD produced an endogenous state that optimized conditions that promote limbic kindling.

Two positive reports on successful open trials with carbamazepine are consistent with the kindling hypothesis. Lipper et al., (1988) observed marked reductions in intensity and frequency of traumatic nightmares, flashbacks, and intrusive recollections among Vietnam combat veterans treated with carbamazepine. Wolf, Alavi, and Mosnaim (1988), also treating Vietnam veterans in an open trial, observed reductions in impulsivity, irritability, and violent behavior. In order to rule out complex partial seizures, which have been postulated to cause PTSD symptoms (Greenstein, Kitchner, and Olsen, 1986; Stewart and Bartucci, 1986), Wolf, Alavi, and Mosnaim (1988) monitored electroencephalograms (EEGs) in conjunction with their carbamazepine protocol; they found that all patients had normal EEGs and none had evidence for complex partial seizures.

Valproate is an antikindling agent that was tested by Fesler (1991) because patients could not tolerate the side effects of carbamazepine (and lithium). Of sixteen Vietnam veterans with PTSD who participated in this open trial of valproate, ten exhibited significant improvement on both hyperarousal and avoidant/numbing symptoms. The other report on valproate is a case report on a single patient whose flashbacks were controlled by valproate (Brodsky et al., 1990).

Lithium

There are uncontrolled reports about lithium's efficacy in PTSD (van der Kolk, 1983; Kitchner and Greenstein, 1985). In an open trial, fourteen out of twenty-two PTSD patients treated with lithium exhibited markedly diminished autonomic hyperarousal, greater capacity to cope with stress, and reduced alcohol consumption. Reporting on these findings, van der Kolk (1987a) stated that this response was clinically indistinguishable from the response to carbamazepine.

It is noteworthy in this regard that among its many complex pharmacological actions, lithium is also an effective antikindling agent. Another pharmacological property of lithium, however, is its enhancement of 5-HT release from nerve terminals, especially in the hippocampus (Treiser et al., 1981).

Serotonergic Agents

Open trials have been reported on three different types of drugs that affect the serotonergic system: fluoxetine, a potent antidepressant serotonin reuptake inhibitor; buspirone, an anxiolytic 5-HT1A partial agonist; and cyproheptadine, a 5-HT receptor antagonist. In addition to theoretical reasons, mentioned earlier, for consideration of 5-HT mechanisms in PTSD, there are also clinical reasons for focusing on serotonergic drugs. A number of symptoms and comorbid disorders seen frequently in PTSD patients may result from serotonergic disruption. These include impulsivity, disinhibition, hostility, depression, obsessive-compulsive behavior, and alcohol and substance abuse/dependency (Yager, 1976; Penk et al., 1981; Branchey, Davis, and Lieber, 1984; Yager, Laufer, and Gallops, 1984; Jelinek and Williams, 1984; Carol et al., 1985; Cloninger, 1987; Hyer et al., 1986; Keane et al., 1988; Kofoed, Friedman, and Peck, 1993).

Fluoxetine is a 5-HT reuptake inhibitor that is a potent antidepressant. Drugs of this type have also been found effective in treating obsessive-compulsive disorder and alcoholism. Davidson, Roth, and Newman (1991) reported successful treatment of five male and female adults with PTSD who had been exposed to industrial/motor vehicle accidents or sexual assault. Treatment was continued for 8–32 weeks, and dosage ranged from twenty to eighty milligrams. In contrast to reports on other drugs, fluoxetine treatment reversed both intrusive and avoidant symptoms. Similar findings were reported by McDougle et al. (1990), who observed marked improvement in avoidant and intrusive symptoms in thirteen of twenty Vietnam combat veterans with chronic PTSD. In a third open trial, Shay (1992a) reported that following fluoxetine treatment, thirteen out of eighteen depressed Vietnam veterans with PTSD exhibited reduced explosiveness and elevated mood.

Buspirone is a 5-HT1A partial agonist with proven efficacy as an anxiolytic. Wells et al. (1991) administered buspirone, thirty-five to sixty milligrams daily, to three combat veterans who fought in World War II, Korea, and Vietnam, respectively. In all cases, anxiety, insomnia, flashbacks, and depressed mood improved following treatment. Unlike trials with fluoxetine, however, buspirone produced no improvement in avoidant symptoms.

Harsch (1986) and Brophy (1991) contributed interesting case reports on two and four PTSD patients, respectively, who received cyproheptadine for traumatic nightmares. In five out of six cases, this 5-HT antagonist successfully suppressed traumatic nightmares within a few days on bedtime doses between four and twenty-eight milligrams. There are additional reports that over eighty patients have now been treated successfully with cyproheptadine for traumatic nightmares

(Michael Brophy, personal communication, 1992). Furthermore, methyergide, a serotonergic antagonist similar to cyproheptadine, has also alleviated sleep and nightmare problems in a small sample of Vietnam veterans with PTSD (Andrew Morgan, personal communication, 1992).

Obviously, more research is needed, especially double-blind clinical trials. These preliminary results are certainly promising and suggest that serotonergic drugs may have an important place in the treatment of PTSD.

Neuroleptics

The pendulum has swung dramatically during the past twenty-five years regarding use of neuroleptics in the treatment of post-traumatic syndromes. During the pre–DSM III (1980) era, before PTSD was classified as a recognized psychiatric syndrome and before it was conceivable that there might be treatable biological alterations in PTSD, clinicians had little conceptual or empirical information to guide them. This was especially true at Veterans Administration (VA) hospitals where Vietnam veterans with (unrecognized) PTSD sometimes appeared to have a bizarre and explosive psychiatric disorder marked by agitation, paranoid thoughts, loss of control, potential for violence, and brief psychotic episodes now called PTSD flashbacks. Symptom relief became the primary goal of treatment. Consequently, neuroleptics were frequently prescribed.

The material reviewed in this chapter indicates that certain biological systems are disrupted in PTSD patients, provides conceptual models suggesting that PTSD has a unique pathophysiology, and suggests through empirical findings that certain drugs may be effective in this disorder. In fact, the pendulum has swung so far in the other direction that there have been no systematic evaluations of neuroleptic treatment for PTSD patients, and none appear to be under serious consideration. After two decades of overuse and misuse, it appears that neuroleptics have no place in the routine treatment of PTSD.

This does not mean that neuroleptics have no place at all in PTSD treatment. Animal research has shown that inescapable stress increases dopamine metabolism in specific mesocortical neurons, especially in the prefrontal cortex (Kalivas and Duffy, 1989). Reports on sexually abused boys (Jensen et al., 1991) and women who had been raped recently (Ende, Gertner, and Socha, 1990) suggest that dopaminergic abnormalities can be detected following traumatization. Finally, clinical reports suggest that neuroleptics may have a specific role in the treatment of refractory PTSD in which patients exhibit paranoid behavior, aggressive psychotic symptoms, overwhelming anger, fragmented ego boundaries, self-destructive behavior, and frequent flashback experiences marked by frank auditory and visual hallucinations of traumatic episodes (Walker, 1982; Atri and Gilliam, 1989; Friedman, 1988). In fact, Mueser and Butler (1987) recommended that neuroleptics be prescribed when PTSD patients present with auditory hallucinations.

In short, the best approach to treatment is to anticipate that TCAs, MAOIs,

and other first-line drugs will attenuate PTSD target symptoms such as hyperarousal and intrusive recollections. Such symptom reduction usually results in amelioration of more dramatic manifestations of this syndrome, such as flashbacks, hypervigilance/paranoia, loss of control, and rage. If these symptoms persist, however, it is time to consider neuroleptic treatment.

CONCLUSIONS

Biological theory and research on PTSD is a dynamic and expanding field. It appears that PTSD is a clinical syndrome that lends itself to a variety of fundamental experimental paradigms, such as inescapable stress, fear potentiated startle, and kindling. In that regard it potentially opens up a wealth of animal research findings for extrapolation to clinical situations.

Biological research with PTSD patients has raised many exciting questions on the pathophysiology of this disorder and on possible pharmacological interventions that may ultimately provide relief of some PTSD symptoms. Although the actual number of publications on neurobiological aspects of PTSD is small, there is an elegant consistency in results from one laboratory to another.

Controlled drug trials, to date, in addition to being few in number, are disappointing in outcome. Not only are the results themselves sometimes inconsistent but effect sizes have often been disappointing in magnitude. It is one thing to demonstrate that drug A is significantly better than drug B from a statistical perspective. It is quite another to say that this statistical difference is important from a clinical perspective.

Future PTSD research will have to address a number of concerns with regard to neurobiological alterations and clinical psychopharmacology. These include lack of standard protocols, lack of standard assessment tools, and failure to control for different comorbid diagnoses (such as depression, alcoholism, substance abuse, and panic disorder) that are frequently found in PTSD patients. Most biological and psychopharmacological research to date has been performed with male veterans exposed to war zone trauma. Future studies must apply the same protocols to women and to individuals exposed to a variety of traumatic situations.

Finally, there is a serious shortage of double-blind drug trials. It is encouraging that the pace of systematic drug evaluation has picked up in recent years and that there are a number of promising results that need further exploration. Given the neurobiological complexity found in animals exposed to inescapable stress and given the evidence from clinical cohorts that is consistent with such animal research findings, it appears likely that a number of interdependent biological systems are disrupted in PTSD. Furthermore, it is also possible that several drugs, each with a different specific action, may need to be prescribed simultaneously to achieve optimal pharmacotherapeutic results in PTSD (e.g., optimal treatment of congestive heart disease often consists of simultaneous prescribing

of complementary drugs such as digitalis, a diuretic, a vasodilator, and a calcium channel blocker). In PTSD, the first suggestion that this may be the case comes from Kinzie and Leung (1989), who found that Cambodian refugees with PTSD had much greater symptom relief from combination treatment with imipramine and clonidine than from either drug alone.

It is apparent from these concluding remarks that researchers have not yet discovered a penicillin or even a lithium for PTSD. Although that remains an experimental and therapeutic goal, other possibilities must be considered. Fortunately, it is abundantly clear that drugs have an important role to play in the current treatment of PTSD, even if they cannot eradicate all of its symptoms. When successful, pharmacotherapy results in attenuation of intrusive recollections and arousal symptoms. Preliminary findings suggest that avoidant/numbing symptoms may also respond to certain drugs. Drug-mediated reduction in intensity of certain target symptoms facilitates psychotherapeutic work on other PTSD symptoms such as impacted grief, guilt, avoidance of emotional expression, problems with intimacy, and moral pain.

In short, medication, at the very least, can be extremely useful as an adjunct to ongoing intrapsychic or behavioral treatment of PTSD. Hopefully, future research will discover single or combination drug treatments that will produce profound improvement in symptom severity and functional capacity for patients who suffer from PTSD.